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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/957,446	09/19/2001	Raphael Marcelpoil	35735/207206	2510

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ALSTON & BIRD LLP
BANK OF AMERICA PLAZA
101 SOUTH TRYON STREET, SUITE 4000
CHARLOTTE, NC 28280-4000

EXAMINER	
UPRETI, ASHUTOSH	
ART UNIT	**PAPER NUMBER**
2623	

DATE MAILED: 10/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/957,446	MARCELPOIL ET AL.	
	Examiner	Art Unit	
	Ashutosh Upreti	2623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-100* is/are pending in the application.

4a) Of the above claim(s) *91-100* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-90* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 September 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

In view of applicant's amendment, the objection to claim 66 is withdrawn.

In view of applicant's amendments, the 35 USC 101 rejections are withdrawn.

Applicant's arguments filed August 22, 2005 have been fully considered but they are not persuasive.

The applicant argues that Lundsgaard (USPN 4,997,769) and Ohta (USPN 5,835,617) either separately or in combination, do not teach or suggest a system involving a color image acquisition device, a plurality of dyes for staining the sample and the analysis of both sample and dye data in the red, green and blue channels of the color image acquisition device.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The applicant seems to be attacking the supporting references for aspects that they were not used for in the initial rejection. **The examiner reminds applicant that these references were not the primary references used in the rejection and that they were combined to teach aspects of the invention not disclosed in the primary reference (the primary reference used was the applicants admitted prior art in the background section of the instant application). The limitations that the**

applicant argues are not in the combination of Lundsgaard and Ohta are found in the primary reference (the applicant's admitted prior art).

The applicant argues that the combination of Lundsgaard and Ohta does not disclose each molecular species being indicated by a dye. This is disclosed in the applicant's admitted prior art (page 3, lines 19-25 particularly lines 19-20 and 24).

The applicant argues that the combination of Lundsgaard and Ohta does not disclose that the indication is from an image of a sample captured by a color image acquisition device in a video microscopy system. This is disclosed in the applicant's admitted prior art (page 5, lines 14-16 and 30).

The applicant argues that the combination of Lundsgaard and Ohta does not disclose that an optical density of the sample is first determined from the image data in each of a red, green and blue channel at a pixel in the image. Obtaining image data in each of a red, green and blue channel at a pixel in the image is disclosed in the applicant's admitted prior art (page 6, lines 2-5). Aspects relating to calculating the optical density are disclosed in Lundsgaard (see the formula in column 1, absorbance and optical density are equivalent here – see the rejection below).

The applicant argues that the combination of Lundsgaard and Ohta does not disclose that the relative absorption coefficient matrix comprises a relative absorption coefficient for each dye, independently of the sample, in each of the red, green and blue channels. Obtaining image data in each of a red, green and blue channel at a pixel in the image is disclosed in the applicant's admitted prior art (page 6, lines 2-5). Aspects

relating to the relative absorption coefficient matrix are disclosed in Ohta (column 12, lines 51-55 – see the rejection below).

The applicant's arguments seem to center mainly on aspects that are disclosed in the primary reference but not in the secondary references. As has been shown above (and in the below rejections) these aspects **are disclosed** in the primary reference. In some cases, the secondary references are used to make up for deficiencies in the primary reference.

The applicant also argues that a person of ordinary skill in the art would not have an objective reason for combining the teachings of the Lundsgaard and Ohta patents. Once again, the examiner notes that the references are not simply being combined together but are actually being combined with the applicant's admitted prior art as they teach some factors that the applicant's admitted prior art does not teach. The applicant fails to mention the applicant's admitted prior art in this regard. The examiner disagrees with the applicant and the reasons for combining the two references with the applicants admitted prior art are given in the applicable rejections. The examiner reminds the applicant that the secondary references are being used simply to highlight information that is well known in the art and that a person of ordinary skill would find obvious to apply to the primary reference. The applicant does for example, claim that because Ohta is directed to computer tomography images, that the reference cannot be used. The examiner points out that this reference is simply being used to show that use of relative absorption coefficient matrices in Lambert-Beer's Law calculations is well known. The applicant also argues that usage of Lundsgaard is inappropriate as the

applicant says that the blood samples are not treated with a dye. The examiner points out that this reference is being used to show that Lambert-Beer's Law is well known and can be applied to microscopy, the applicant's argument is therefore directed at something for which the reference is not being used.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 11, 26-28, 36-38, 41, 42, 50-52, 55, 64-66, 72-74, 77, 78, and 86-88 are rejected under 35 U.S.C. 103(a) as being unpatentable over the applicant's admitted prior art in view of Lundsgaard (U.S. Patent 4,997,769) and further in view of Ohta (U.S. Patent 5,835,617).

As to claim 1, The background of the instant application discloses determining an amount of at least one molecular specie comprising a sample (page 1, line 7), each molecular specie being indicated by a dye (page 3, line 24), from an image of the sample captured as image data by a color image acquisition device in a video-microscopy system (page 5, lines 15-16 and 30). The background of the instant application also discloses obtaining data in each of a red, green and blue channel, for pixels in the image (page 6, lines 2-5).

The background of the instant application does not expressly disclose determining an optical density of the sample from the image data so as to form a corresponding optical density matrix for the pixel; and multiplying the optical density matrix by an inverse of a relative absorption coefficient matrix so as to form a resultant matrix for the pixel, the relative absorption coefficient matrix comprising a relative absorption coefficient for each dye, independently of the sample, in each of the red, green, and blue channels, the resultant matrix comprising the amount of each molecular specie, as indicated by the respective dye, for the pixel.

Lundsgaard discloses determining an optical density of the sample from the image data; and dividing the optical density by the absorption coefficient so as to form a resultant, the absorption coefficient obtained, independently of the sample (column 2, lines 44-45 – here the absorption coefficients are predetermined and are therefore considered to have been obtained independently), in each of the channels (column 2, lines 46-47 – here image data at each individual wavelength is equivalent to a channel), the resultant comprising the amount of each molecular specie (column 2, line 33 – here concentration is determined, which is equivalent to the amount of the specie). Lunsgaard discloses what is shown overall above, by showing the use of Lambert-Beer's law (column 1, lines 31-36). As concentration is the term being solved for (column 1, lines 32-33), the other terms are must be being determined prior to solving. Note that this is equivalent to the equation used in the instant application (page 12, equation 1), as absorbance and optical density are equivalent terms in this case. The equation can then be rearranged so as to show that the amount of molecular specie is

obtained by dividing the optical density by the absorption coefficient, as shown in the instant application (page 24, line 9). When dealing with matrices, instead of division, multiplying by the inverse is used. The use of matrices is inherent when using equations on a computerized system dealing with images as images themselves are treated as matrices by computers. Lundsgaard further discloses matrix usage (column 1, lines 56-62 – here solving "number of linear equations" is equivalent to a matrix).

It would have been obvious to a person of ordinary skill in the art, at the time the invention was made, to use Lambert-Beer's law as disclosed in Lundsgaard when processing the image data from each of the color channels in the applicant's admitted prior art as they both deal with finding concentrations of biological components in a specimen. This would result in improved identification of optical density of the sample and/or dye, thus providing motivation.

The combination of the applicant's admitted prior art and Lundsgaard as applied above does not expressly disclose the use of a relative absorption coefficient matrix in Lambert-Beer law calculations.

Ohta discloses the use of a relative absorption coefficient matrix (column 12, lines 51-55) in Lambert-Beer law calculations.

It would have been obvious to a person of ordinary skill in the art, at the time the invention was made, to use a relative absorption coefficient matrix as in Ohta when calculating the amount of a molecular specie as in the applicants admitted prior art and Lundsgaard, as they both involve Lambert-Beer law calculations. Doing so would

provide a basis for more accurate comparison of data from different color channels, thus providing motivation.

As to claim 14, as to use of a counterstain, the examiner takes official notice that use of a counterstain is well known in the art of microscopy. It would have been obvious to a person of ordinary skill in the art to use a counterstain as they are commonly used to color the components in a microscopic specimen that are not made visible by the principal stain, thereby improving the visibility of those components.

As to claims 26, 41, 55, 64 and 77, the limitations of the claims are rejected for the same reasons as in the rejection of claim 1.

As to claim 11, the applicants admitted prior art as modified above, further discloses capturing an image of the sample as image data in each of the red, green, and blue channels of at least one of an RGB camera and an RGB-configured scanner (page 2, line 18 and page 6, lines 1-2).

As to claim 27, the limitations of the claim are rejected for the same reasons as in the rejection of claim 11.

As to claim 28, Lundsgaard as applied above, further discloses determining an initial intensity of a light emitted by a light source (column 1, line 49) in each of the red,

green, and blue channels (values at specific wavelengths of light are able to be determined as shown in column 1, lines 40-41).

As to claims 36, 37 and 38, Lundsgaard as applied above further discloses computer storage media and processors (column 4, lines 17-20) used for calculating concentration (column 4, line 14). The more detailed aspects of the calculations such as involving relative absorption coefficients and matrices have been discussed in the rejection of claim 1 and the aspects involving doing these calculations for the dyes have been discussed in the rejection of claim 2.

As to claims 50, 51 and 52, the limitations of the claims are rejected for the same reasons as in the rejections of claims 36, 37 and 38 respectively.

As to claims 72, 73 and 74, the limitations of the claims are rejected for the same reasons as in the rejections of claims 36, 37 and 38 respectively.

As to claims 86, 87 and 88, the limitations of the claims are rejected for the same reasons as in the rejections of claims 36, 37 and 38 respectively.

As to claim 42, the applicants admitted prior art as modified above further discloses a computer directing a light source to illuminate the sample with a light having

an initial intensity in each of the red, green, and blue channels (page 2, lines 19-22 indicate automated light control and page 6, lines 1-2 discuss RGB channels).

As to claim 78, and the limitations of the claim are rejected for the same reasons as in the rejection of claim 42.

As to claim 65, the applicants admitted prior art as modified above, discloses a light source directed toward the RGB camera (page 6, lines 9-11 – if an image is captured by the RGB camera, then light must be directed towards it) and configured to emit a light having an initial intensity in each of the red, green, and blue channels (see the rejection of claim 42).

As to claim 66, the examiner takes official notice that it is well known in the art to illuminate a microscopy sample with light when capturing its image with a camera. It would have been obvious to a person of ordinary skill in the art to illuminate a microscopy sample as good lighting is required for accurate color imaging and illumination would therefore enable a more accurate image. Regarding determining an optical density being further configured determine a transmitted intensity of the light transmitted through the sample in each of the red, green, and blue channels of the RGB camera, see the rejection of claims 1 and 43.

Claims 12, 13, 24, 25, 39, 40, 46, 53, 54, 68, 75, 76, 89, and 90 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of the applicant's admitted prior art and Lundsgaard and Ohta as applied to claims 1, 14, 26, 41, 55, 64 and 77 above, and further in view of Krasieva (U.S. Patent 5,734,498).

As to claim 12, the combination of the applicant's admitted prior art and Lundsgaard and Ohta does not expressly disclose illuminating the sample under Koehler illumination conditions.

Krasieva discloses disclose illuminating the sample under Koehler illumination conditions (column 7, line 48).

It would have been obvious to a person of ordinary skill in the art, at the time the invention was made, to use Koehler illumination as in Krasieva for illuminating the sample in the combination of the applicant's admitted prior art and Lundsgaard and Ohta as they both involve examining specimens by microscope and doing so would ensure ample light for illuminating the sample as taught by Krasieva (column 5, lines 21-22).

As to claims 24, 39, 53, 75 and 89, the limitations of the claims are rejected for the same reasons as in the rejection of claim 12.

As to claim 13, the combination of the applicant's admitted prior art and Lundsgaard and Ohta does not expressly disclose correcting chromatic aberration in the video-microscopy system.

Krasieva discloses correcting chromatic aberration in the video-microscopy system (column 11, lines 53-54).

It would have been obvious to a person of ordinary skill in the art, at the time the invention was made, to correct for chromatic aberration as in Krasieva when imaging specimens as in the combination of the applicant's admitted prior art and Lundsgaard and Ohta as they both involve color imaging of specimens by microscope and doing so would reduce the amount of inaccuracies in the images.

As to claims 25, 40, 54, 76 and 90, the limitations of the claims are rejected for the same reasons as in the rejection of claim 13.

Claims 2-10, 15-23, 29-35, 43-49, 56-63, 67-69, 70, 71, and 79-85, are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of the applicant's admitted prior art and Lundsgaard and Ohta as applied to claims 1, 14, 26, 41, 55, 64 and 77 above, and further in view of Stone (U.S. Patent 6,819,787).

As to claim 2, the combination of the applicants admitted prior art and Lunsgard and Ohta, as applied above, discloses the use of a relative absorption coefficient matrix instead of just an absorption coefficient matrix (see rejection of claim 1).

The combination of the applicants admitted prior art and Lunsgard and Ohta, does not expressly disclose determining the relative absorption coefficient for each dye, independently of the sample, in each of the red, green, and blue channels.

Stone discloses determining the absorption coefficient for each dye (column 8, lines 43-44 and 56 show that the absorption coefficient of the dyes are determined), independently of the sample (column 6, line 47 – non-tissue area means independent of the tissue sample), in each of the red, green, and blue channels (column 6, lines 45-46).

It would have been obvious for a person of ordinary skill in the art, at the time the invention was made, to determine the absorption coefficients of each dye independent of the sample as in Stone, when calculating the amount of a molecular specie as in the combination of the applicant's admitted prior art and Lundsgaard and Ohta, as they both process microscopy images of stained biological samples. Doing so would enable the effects of the dye to be subtracted from the overall image, leaving only the effects of the sample, thus providing motivation.

As to claim 15, Stone further discloses conducting the above-mentioned calculations for a second stain present in the sample (column 8, lines 56-57). The counter stain is considered to be a second dye/stain in the sample. All other limitations are rejected for the same reasons as in the rejection for claim 2.

As to claim 56, the limitations of the claim are rejected for the same reasons as in the rejection of claim 2.

As to claim 3, 16 and 57, the limitations of the claims are rejected for the same reasons as in the rejection of claim 28.

As to claim 4, Stone as applied above, further discloses illuminating each dye with the light source, independently of the sample (column 6, lines 45-48 show that the background areas are being illuminated – these are the areas where only the dyes are present, independent of any tissue), and determining a transmitted intensity of the light transmitted therethrough in each of the red, green, and blue channels (column 6, equation 1 on line 63).

As to claims 8, 17, 21, 29, 32, 46, 58, 68 and 82, the limitations of the claims are rejected for the same reasons as in the rejection of claim 4.

As to claim 5, the combination of the applicant's admitted prior art and Lundsgaard and Ohta does not expressly disclose comparing the initial intensity of the light to the transmitted intensity of light so as to determine an optical density for each dye in each of the red, green, and blue channels.

Stone as applied above, further discloses comparing the initial intensity of the light to the transmitted intensity of light so as to determine an optical density for each dye in each of the red, green, and blue channels (column 8, lines 62-67).

It would have been obvious for a person of ordinary skill in the art, at the time the invention was made, to use initial intensity and transmitted intensity of light to determine optical density of each dye as in Stone, when calculating the amount of a molecular specie as in the combination of the applicant's admitted prior art and Lundsgaard and

Ohta, as they both process microscopy images of biological samples stained with dyes. Doing so would enable the effects of the dye to be subtracted from the overall image, leaving only the effects of the sample, thus providing motivation.

As to claims 9, 18, 22, 30, 33, 44, 47, 62, 69 and 83, the limitations of the claims are rejected for the same reasons as in the rejection of claim 5.

As to claim 6, Stone as applied above, further discloses determining an optical density for each dye by determining a natural logarithm of a ratio of the initial intensity of the light to the transmitted intensity of the light in each of the red, green, and blue channels (see rejection of claim 5 and column 9, lines 26-31).

As to claims 10, 19, 23, 31, 34, 45, 48, 59, 63, 67, 70, 81 and 84, the limitations of the claims are rejected for the same reasons as in the rejection of claim 6.

As to claim 7, the examiner takes official notice that it is well known in the art to normalize the optical density in each of the red, green, and blue channels, with respect to the channel having the highest optical density.

It would have been obvious for a person of ordinary skill in the art, at the time the invention was made, to normalize the channel optical density data with respect to the channel exhibiting the highest optical density, in the data for each dye, as determined in the combination of the applicants admitted prior art and Lundsgaard and Ohta and

Stone. This would allow for more accurate data comparison between channels, thus providing motivation.

As to claims 20, 35, 49, 60, 71 and 85, the limitations of the claims are rejected for the same reasons as in the rejection of claim 7.

As to claim 43, Stone as applied above, further discloses a computer directing a measurement (column 5, line 48) of a transmitted intensity of the light transmitted through the sample in each of the red, green, and blue channels (column 9, lines 16-19 and column 8, lines 48-50).

As to claim 61, and the limitations of the claim are rejected for the same reasons as in the rejection of claim 66.

As to claim 79, and the limitations of the claim are rejected for the same reasons as in the rejection of claim 43.

As to claim 80, the combination of the applicant's admitted prior art and Lundsgaard and Ohta does not expressly disclose determining an optical density is further capable of comparing the initial intensity of the light to the transmitted intensity of the light so as to determine an optical density for the sample in each of the red, green, and blue channels of the RGB camera.

Stone as applied above discloses that determining an optical density is further capable of comparing the initial intensity of the light to the transmitted intensity of the light so as to determine an optical density (column 8, lines 63-67) for the sample in each of the red, green, and blue channels of the RGB camera (column 9, lines 26-29 – here optical density for every point in the image is calculated, which therefore includes the sample).

It would have been obvious for a person of ordinary skill in the art, at the time the invention was made, to use initial intensity and transmitted intensity of light to determine optical density of a sample as in Stone, when calculating the amount of a molecular specie as in the combination of the applicant's admitted prior art and Lundsgaard and Ohta, as they both process microscopy images of biological samples stained with dyes. Doing so would enable optical density to be calculated, thereby allowing the amount of the sample to be more accurately measured, thus providing motivation.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ashutosh Upreti whose telephone number is (571) 272-7428. The examiner can normally be reached on Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jingge Wu can be reached on (571) 272-7429. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AU

AU
October 11, 2005

JINGGE WU
PRIMARY EXAMINER